Lymphoma

Cutaneous Malignant Lymphoma

• Poikiloderma atrophicans Vasculare •

PAV

Eruption & 3 clinical components:

3
1- mottled Hypo-Hyper pigmentation
2- Telangiectasia
3- Atrophy Develop at later stages

Causes:-

- PAV not an independant dermatosis
- poikiloderma like lesions Can seen in 3 diffrent occasions

3
1- Genodermatosis
   - poikilodema congenitale of Rothmund Thomson
   - Bloom's syndrome
   - Dyskeratosis Congenita
2- Early stage of MF
3- Autoimmune CT disease • late stage Dermatomyositis • less common SLE

Histopathology:

Early stage
- Flattened Epidermis with hydropic Degeneration of Basal cells
- The upper dermis → Band-like infiltrate
- Invade Epidermis & Melanophages
- pigmentary incontinance
- edema
- Capillary dilation

Late Stage
- The amount of infiltrate Varies & the Cause:
  - Genodematoses DM, SLE → Infiltrate → mild
  - in MF → infiltrate ↑↑ & Mycosis Cells and epidermotropism

• poikiloderma of Civatte •

→ lesion: Reddish-Brown Reticulate pigmentation
→ with telangectasia - atrophy
→ Symmetrically develop on:
  ↳ lateral cheeks
  ↳ side of neck -
→ occur in:
middle age female in menopusal stage (D.t endocrinal factor)
or D.t → light exposure
OR → photodynamic substances

• Parapsoriasis •

Ⓐ D.f: very chronic, Asymptomatic Heterogenous group of Disorders which include:

I pityriasis lichenoids

a- pityriasis lichenoides et variliformis acuta

b- pityriasis lichenoides chronica (Juliusberg)

II parapsoriasis en plaques :-

- small plaque parapsoriasis + large plaque
- Idiopathic, chronic Dermatoeses

Ⓐ pathogenesis :

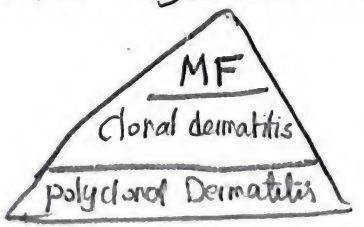
◎ Dominant T. cell → in many cases of Large plaque parapsoriasis, Fewer Cases of small plaque

◎ concept of- "Clonal dermatitis" :-

↳ T. cell lymphoproliferative Disorders → intermediate or transitional step Between → Chronic Dermatitis and over Cutaneous T. cell lymphoma

↳ clonal dermatitis is 20%, Risk of progression to Cutaneous T-cell lymphoma Over 5 yrs

↳ Example of clonal Dematitis :-
- Small plaque
- Large plaque parapsoriasis
- Some cases of primary idiopathic erythroderma
- Chronic Dematitis



Small plaque type :-

→ Small (1-5cm in diameter)
→ pink - yellow oval - non-Itchy patches & distinct Borders and Covered with : fine pityriasiform Scales
→ Symmetrically distributed over the trunk and proximal portions of the extremities
→ Very chronic Disorder that may persist for years.

Variants :-

① Xantho-erythroderma Perstans : Yellow hue
② Digitate Dermatosis :
- finger-like patches
- Symmetrically on flanks
- measure 10cm or more along Their Long axis

Histopathology :

- non-specific perivascular lymphocytic infiltrate
- exocytosis - spongiosis - acanthosis
- parakeratosis.

Large plaque Type

→ The patches are Larger >5 cm in diameter
→ Poorly defined , Non-Itchy
→ Covered : fine superficial scales
→ atrophy or poikiloderma → may develop.

Variants :-

① Poikilodermatous variant : associated triad of poikiloderma
② Para-psoriasis variegata : (البرقي)
[Parakeratosis variegata :
Retiform parapsoriasis]
- extensive network of Retiform eruption of lichenoid Papules with deeply erythematous patches and poikilodermatous changes

Histopathology :

① Early → non specific dermatitis ② later on : poikilodermatous changes occur : → Band-like dermal infiltrate → invade The epidermis , Flattened epidermis , Hydropic degeneration of Basal Cells

③ with transformation to lymphoma :- abnormal cells present Both in the dermal infiltrate and in Epidermis.

✱ Relation to Lymphoma:

Small plaque
- Benign disorder
- not related to MF

large plaque
- Clinical
  - Transition to MF occur in 12%.
- histological
  Transition to MF → 50%.

✱ Treatment:

→ Small plaque → Follow-up

→ Large plaque → parapsoriasis should be treated

↳ **Standard therapy:**
- Topical Corticosteroids
- Topical col tar products
- Phototherapy
- Bexarotene
- Calcineurin inhibitors
- Imiquimod

↳ **Cases of large plaque parapsoriasis That meet the Histopathological Critria of MF :-**

--treated as early MF

↳ Topical Corticosteroids
↳ Phototherapy
↳ Topical Mechlore-thamine (nitrogen mustard)
↳ Topical Carmustine (BCNU)
↳ Topical Bexarotene
↳ Subcutaneous interferone-α
↳ expiremental therapies :-
- IL-12
- examer laser 308 nm

Cutaneous T-cell lymphoma

- Cutaneous Malignant lymphoma :-
  malignant neoplasia of lymphatic system
- Classification :-

Cutaneous T-Cell lymphoma
CTCLs
Derived from T-lymphocytes

B-Cell lymphoma
Derived from B-lymphocytes

Non-B cell Non-T cell lymphoma
- Hodgkin's Disease
- Blastic plasmacytoid dendritic cell neoplasm.

- Cut. T. cell lymphomas

Cutaneous T-cell Lymphomas "CTCLs"

WHO-EORTC classification for cutaneous T-cell lymphomas

WHO-EORTC classification	Frequency (%)*	5-year survival rate (%)*
Indolent clinical behavior		
Mycosis fungoides (MF)	54	88
Mycosis fungoides variants & subtypes		
• Primary cutaneous anaplastic large cell lymphoma (C-ALCL)	6	80
• Lymphomatoid papulosis (LyP)	1	100
• Granulomatous slack skin	<1	100
Primary cutaneous CD30-positive lymphoproliferative disorders		
• Primary cutaneous anaplastic large cell lymphoma (C-ALCL)	10	95
• Lymphomatoid papulosis (LyP)	16	100
Subcutaneous panniculitis-like T-cell lymphoma (SPTCL)	1	82
Primary cutaneous CD4-positive small/medium pleomorphic T-cell lymphoma‡	3	75
Aggressive clinical behavior		
Sézary syndrome (SS)	4	24
Adult T-cell leukemia/lymphoma (ATLL)	NDA	NDA
Extranodal NK/T-cell lymphoma, nasal type	1	<5
Primary cutaneous CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma‡	<1	18
Primary cutaneous gamma/delta T-cell lymphoma (PCGD-TCL)‡	1	<5
Primary cutaneous peripheral T-cell lymphoma (PTCL), unspecified§	3	16

Mycosis fungoides

• **DF:** uncommon, Chronic, slowly progressive, fatal, Malignant lymphoma of T- helper cell-Type

• affect skin first → for many years.
later → can affect the lymph nodes and internal organs:
↓
Develop after age of 40 yrs.

• **Clinical features**

① Premycotic Stage:

1- non-atrophic patchy eruptions
2- Simulating various forms of Dermatitis or psoriasis
3- generally → followed By infiltrated plaque within several months or yrs
4- clinical ch.ch →
• persistant pruritus Not Relived By ordinary ttt
• Reticulation • Bizarre configuration
• polymorphism • Vivad coloration
5- many clinical entities: → progress after vaiable latent Period to overt MF:
e.g: Large plaque Type of parapsoriasis

② plaque Stage:

1- Sharply demarcated, Slight indurated plaques
2- Erythematous oR violaceous in color
3- Coalescence of adjacent lesions with central Resolution → "Geographic apperance"
↓
(Islands of normal skin)
4- marked Pruritis

(III) Tumor Stage :-

→ multiple - non pruritic - dome - irregular - shaped - flesh colored

→ soft Tumors è Nodular or eroded surfaces

→ appearing in the infiltrated or normal skin

undergo Ulceration

in This stage → may pts show defect in CMI Responses

⑤ D'emblée form of MF :

- Tumors appear without previous Erythematous or plaque lesions.
- Some of these lesions may Be : B-Cell lymphoma Rather than true MF

⑥ 15% of Alopecia mucinosa → associated è CTCL

Histopathology :-

① Premycotic Stage :-

- Non specific
- Presence of Epidermotropism

② Plaque Stage :

Polymorphous Cellular infiltrate
- Histiocytes
- eosinophils
- lymphoid cells
- plasma cells

↓ in Band-like pattern in Upper dermis

Mycosis Cells
- in the dermal infiltrate
- they are → T. lymphocytes with hyper-chromatic and irregulary shaped Nuclei

Epidermotropism (Diagnostic)
- Scattered mono nuclear cells

↓ Surrounded By :- halo within the Epidermis without Spongiosis

- pautrier - micro Abscesses

↓ small intra-epidermal groups of mono-nuclear cells Located within Vacuole

③ Tumor Stage :

- large masses of Mycosis cells → extend into SC. fat
- Epidermotropism
- pautrier microabscess → Rarely seen
- the infiltrate Shows → many Cells è blastic transformation

Extracutaneous involvment:

- High incidence of extracut. affection → in Autopsy
- clinically apparent visceral affection → Rare
- At Autopsy:
  - ↳ The most frequent site of extra cut. lesion → lymph nodes 75%. liver 53%. Lungs 60%. spleen 60%.
  - Circulating Sezary Cells → 12-20% of the ptn's Concentration <15%.

Prognosis:-

1- in premycotic stage → ptn Survive for many yrs (5-20 yr) (5yr average)

2- The prognosis is Unfavorable if Tumors LN, Visceral involvement occur

3- Death occur D.t → Systemic infection or disseminated organ involvement

pathogenesis:-

① plaque. Tumor stages → Represent a Malignant Lymphoma:- in which → mycosis cells (T lymphocyte) is The neoplastic cell

② There are two theories for The initial Stage:
- 1. MF is a malignant process from its beginning
- 2. MF starts as immunologic Disorder and only Later → Develop into a Lymphoma-

Etiology:-

3 Current theories present for etiology

(A) Genetic factors

- accumulation of genetic abnormalities → Result in Clonal proliferation, malignant Transformation, progressive and widely disseminated disease

(B) Environmental Factors:-

1- Antigen persistence → Presence and persistance of unknown antigen → Chronic stimulation and proliferation of T-cells ⟹ Malignant Transformation after a period of time

- The presence of large number of LCs in early lesions of MF → support Theis theory
- The LCs (OkT6) → found throughout epidermis → (in) pautrier microabscess and in the dermal infiltrate in close apposition to lymphoid cells

2- Viral Relationship →

- HTLV-1 antibodies → found in 11%

3- Relationship to industrial exposure to Carcinogens.

(C) Immunological Factors:-

1- The neoplastic T cells in Sézary syndrome and in Tumor stage MF :-
Derived from CD_4 + T-cells.

2- CD_8 + Cytotoxic T-cells : play Crucial Role

3- gradual shift from a predominantly Type 1 cytokine profile in MF plaques → to predominantly Type 2 cytokine profile in MF Tumors

4- ↑↑ level of Th2 cytokines → impair the Th1 cell mediated antitumor response and Contribute to the immunosuppression seen in: ptn's advanced MF

• Diagnostic techniques

1. lymphocyte surface membrane markers :-

- The majority of lymphocytes seen in the MF lesions → bear The CD_4 antigen ⇄ which is the marker of T-helper subset and small propoition of CD_8 +ve T-suppressor subset (2:1)

- This pattern is Not specific to MF. and found in many benign inflammatory Dermatoses

[2] DNA Cytophotometry:-

- cls malignant cells → Contain a Hyper-tetraploid DNA content
- Their detection maybe of value in Early Diagnosis of MF.

[3] Measurment of lymphocyte Nuclear Contour index (NCI)

- During electron microscopic exam

[4] Analysis of T-cell Receptor Gene rearrangement TCRGR:-

- By Southern blot hybridization

• Variants of MF:

① Classical: Alibert-Bazin Type

② Bullous, Hypo-Hyper pigmented MF; clinical Behavior similar to classic MF-

③ Folliculotropic, Pagetoid reticulosis, granulomatous slack skin variants

	Folliculotropic MF	Pagetoid reticulosis (Woringer-Kolopp disease)	Granulomatous slack skin
Definition	Characterized by the presence of folliculotropic infiltrates, often with sparing of the epidermis & preferential involvement of the head & neck region.	Localized patch or plaque with an intraepidermal proliferation of neoplastic T-cells.	Characterized by the slow development of folds of lax skin & a granulomatous infiltrate with clonal T-cells.
Clinical picture	• Grouped follicular papules, acneiform lesions, indurated plaques & sometimes tumors. • Commonest sites: Head (often associated with alopecia) & neck area. • Pruritus is often more severe than in classical MF.	• Solitary psoriasiform or hyperkeratotic patch or plaque on an extremity. • No extracutaneous dissemination or disease-related deaths.	Circumscribed areas of pendulous lax skin with a predilection for the axillae & groin.
Histopathology	Perivascular & periadnexal localization of neoplastic cell with variable infiltration of the follicular epithelium.	Hyperplastic epidermis with marked infiltration by large atypical pagetoid cells, arranged singly or in nests or clusters.	• Dense granulomatous dermal infiltrates containing atypical T-cells. • Destruction of elastic tissue & elastophagocytosis by the multinucleated cells. • The epidermis is infiltrated by small atypical T-cells.
Preferred treatment	Total skin electron beam irradiation.	Radiotherapy or surgical excision.	Radiotherapy may be effective.

Treatment of mycosis fungoides (Fig. 22)

Premycotic phase

- Topical or intralesional corticosteroids; UVB.
- If former not effective, PUVA.

Stage IA-IIA (patches/plaques)

- PUVA; topical nitrogen mustard; topical carmustine.
- UVB (if only patches).
- Topical corticosteroids or topical bexarotene (if only limited patches/thin plaques as second-line therapy).
- Local radiotherapy (RT) (if single lesion).
- Total skin electron beam (TSEB) (if generalized thick plaques).

Stage IIB (skin tumors)

- PUVA or topical nitrogen mustard + RT (if only a few tumors).
- TSEB (followed by skin-directed therapies).
- Relapse: PUVA + IFN-α; PUVA + retinoids (acitretin; oral bexarotene*); second-line therapy: Denileukin diftitox*; HDACi*.
- Add RT (if persistent tumors); consider second course of TSEB (10-20 Gy).

Stage III (erythroderma)

- Extracorporeal photopheresis; if not effective, add IFN-α.
- Low-dose chlorambucil & prednisone; low-dose methotrexate.
- Add skin-directed therapies (PUVA; topical nitrogen mustard; RT), if necessary.
- Second-line therapy: Oral bexarotene*; denileukin diftitox*; HDACi*.

Stage IV (nodal, visceral involvement)

- Multi-agent chemotherapy (e.g. CHOP).
- Biological response modifiers (denileukin diftitox; IFN-α; oral retinoids).
- Add skin-directed therapies (PUVA; topical nitrogen mustard), if necessary.
- Allogeneic hematopoietic stem cell transplantation (in selected cases).

Sézary Syndrome

- Ch.ch By triad: 3

(1) Generalized Erythroderma with edema and intense Itching may start denove or follow MF lesion

(2) Peripheral Lymphadenopathy
- Hepatomegaly, Alopecia
- onychodystrophy - palmoplantar Keratoderma

(3) ATypical mononuclear Cells "Sezary cells" in the skin and peripheral Blood with moderate leukocytosis

- The concentration of atypical mononuclear cells 15-30% of WBCs (>1000/mm³).
- They originate from the skin or from lymph nodes
- They may present in
  - Dermatitis
  - psoriasis
  - actinic Reticuloid
  - BCC
  - DLE
  - CBCLs

  Lp ← Parapsoriasis ← lymphomatoid papulosis ← over Healthy ppl.

  But concentration <15%.

"Sezary phenomenon"

Criteria Recommended for the Diagnosis of SS"

1- T-Cell Clone in the peripheral Blood By molecular or Cytogenetic methods

2- Immunophenotypical abnormalities (expanded CD4+ T-Cell population Result in → CD4/CD8 ratio >10 and aberrant expression of pan-T cell antigen)

3- Absolute Sezary cell count at least 1000 cells per μL

Pre-Sezary Syndrome

- Erythroderma with No specific histologic features and Few Sezary cells Below 1000/mm³
- Some Cases may evolve To Sezary

in the WHO-EORTC classification :-

- demonstration of T-Cell clone in Combination with one of the aforementioned immunophenotypical Critriea :- are suggested as minimal Criteria for the diagnosis of SS
- So as to exclude ptn & a benign inflammatory Condition simulating SS.

Histopathology :-

- simulate MF , But → in some ptns Epidermotropism and pautrier microabscesses → Absent
- may be Grenz Zone of normal dermis → separating the dermal infiltrate from epidermis

- Treatment :

1- extracorporeal photopheresis (ECP) and other ttt modalities (ttt of choice).

2- IFNα - PUVA Therapy → prolonged ttt with Low-dose chlorambucil + prednisone or MTx

3- CHOP - CHOP-like regimens

4- other options: Bexarotene, denileukin diffitox, HDACi - denituzumab

5- Skin-directed therapies: - like PUVA or potent topical corticosteroids.
(adjuvant therapy)

Comparison of subcutaneous panniculitis-like T-cell lymphoma and primary cutaneous γ/δ T-cell lymphoma with subcutaneous involvement [11]

	SPTCL	PCGD-TCL with subcutaneous involvement
Phenotype	α/β T cell phenotype.	γ/δ T-cell phenotype.
T-cell receptor	βF1+, TCRδ1-	βF1-, TCRδ1+
T-cell phenotype	CD3+, CD4-, CD8+	CD3+, CD4-, CD8-
Coexpression of CD56	Absent	Common
Architecture	Subcutaneous.	Subcutaneous & epidermal/dermal
Clinical features	Nodules & plaques, rarely ulceration.	Nodules & plaques. Ulceration common.
Hemophagocytic syndrome	Uncommon	Common
Survival (5-year)	>80%	<10%
Treatment	Systemic corticosteroids.	Systemic chemotherapy.
WHO-EORTC classification (2004) WHO classification (2008)	Subcutaneous panniculitis-like T-cell lymphoma.	Primary cutaneous gamma-delta T-cell lymphoma.

• Sub-Cutaneous Panniculitis Like T-Cell Lymphoma SPTCL

D.f: Cytotoxic T-cell lymphoma

ch.ch By: presence of lrg subcutaneous infiltrates of: - Small-medium-large pleomorphic T-cells with an α/β + T-cell phenotype. in association è many macrophages

• Adult T-cell Leukemia / Lymphoma

- **Epidemiology:**
  - Caused By: retrovirus human T-cell lymphotropic virus (HTLV-1)
  - endemic in: Japan, Caribbean Islands
- **Transmission:**
  - Sexually – Blood products – Breast Feeding
- **Clinicall:**
  - after latency period → There is the Carrier state
  - ↳ Ch·ch By: –ve HTLV-1 antibody, No Circulating abnormal cells
  - After this stage :- widespread papules, plaques, tumors or Erythroderma occur.
  - lymphadenopathy, Bone pain Due to: Osteolytic lesions and Hypercalcemia.
- **Histopathology:**
  - Dermis → Infiltrated By → multiple aggregates of Atypical Lymphocytes with formation of intraepidermal focal aggregates of These cells "Pautrier microabscess"
  - Circulating malignant cells "Sezary Cells" :- easily Recognized.
  - ch·ch finding: very high level IL-2 receptor (Tac) gene expression by peripheral Blood and skin infiltrating lymphocytes

• Primary Cutaneous CD30 +ve lymphoproliferative disorders •

- primary Cutaneous CD30 +ve → Represent The 2nd most common group of CTCL (25% of CTCL)
- Primary cutaneous anaplastic and non-anaplastic CD30+ large cell lymphoma
- Lymphomatoid papulosis
- Borderline Cases :-
  - → Regressing atypical histiocytosis
  - → Regressing phase anaplastic lymphoma
  - → Eosinophilic Histiocytosis

↳ pleomorphic giant lymphomatoid papulosis
↳ lymphomatoid papulosis - diffuse large cell type

- Primary Cut. Hodgkins disease

- chch By :

1 Clinnically:

- Occur in adults
- solitary or Localized skin lesion
- Infrequent spontenous Remission
- Rare :- extra Cut. involvement as (L.N)
- High Responsive to Radiotherapy
- Favorable prognosis

2 Histology - Immunohistochemistry

- Dense non-epidermotropic infiltrate of large CD30+ tumor cells with round-oval - irregularly Shape nuclei
one or Several prominant eosinophilic nucleoi - abundant cytoplasm
- mitotic figures → numerous
- Immunophenotypic and gene rearrangment Studies show: most of these Iry Cutaneous CD30+ LCLs are T-cell origin
- These Iry Cut CD30+ve LCLs → are part of a continuous spectrum of primary Cut CD30+ve lymphoproliferative disorders which include: ↳ Lymphomatoid papulosis
↳ Borderline Cases

DD between cutaneous CD30+ large cell lymphoma, borderline cases & lymphomatoid papulosis (LyP) HL

Features	CD30+ LCL	Borderline	LyP
Clinical			
Lesions	Nodule, tumor	Nodule	Papules>nodules
Extent	Solitary>regional (rarely diffuse)	Regional	Regional/diffuse
Spontaneous remission	Infrequent	Frequent	Always
Extracutaneous disease	25%	Absent	Absent
Histologic			
Wedge-shaped infiltrate	Absent	Occasional	Regulary
CD30+ cells	Large sheets	Small clusters	Scattered
Infiltration of subcutis	+	-	-

Lymphomatoid papulosis

- **D.f** = chronic - clinically Benign dermatosis with histologic features → suggestive :- malignant lymphoma.
  - 10% of ptn lymphoma develop as Hodgkins or non-Hodgkins

- **Clinical features :-**
  - ch.ch By: chronic - asymptomatic, Recurrent Crops
  - each last: 2-8 weeks
  - self-healing papulonecrotic or papulonodular lesions.
  - mainly on: Trunk, extremities
  - There are 2 patterns:
    - ① PLEVA-like lesions: Erythematous papulovesicular lesions → Become Hemorrhagic OR Necrotic
    - ② Dusky erythematous larger papules - nodules → tendency to Coalesce
  - Healing → with Hyperpigmented or atrophic Scars

- **Histopathology :-**
  - epidermal spongiosis • exocytosis
  - Epidermotropism
  - The Dermis show : Dense, patchy, wedge-Shape perivascular - polymorphus infiltrate of → Neutrophils → eosinophils → mononuclear cells Large, hyperchromatic irregulary shaped nuclei & atypical appearance. ← ch.ch By

- 3 types :- known histologically :-

Type A
histiocytic
- Large Atypical CD30+ve cells
- Simulating :- Reed-Sternberg cells
- Esinophils -- Neutrophils → numerous

Type B
Lymphocytic
- Small ATypical CD30 -ve Cerebriform mono-nuclear cells
- Similar to Those of MF
- eosinophils -- Neutrophils → Less numerous
- Epidermotropism → Early feature

Type C
as C-ALCL
- Large clusters of large CD30+ T-cells
- Few admixed inflammatory cells

- **Treatment :**
  - Low Dose weekly → Methotrexate
  - PUVA
  - High potency Topical Steroid
  - Topical Nitrogen mustard

• Treatment options of CTCL •

⋆ Skin Targeted therapy ⋆

① Topical Corticosteroids :
- effective in controlling Disease activity in patch/plaque stage Disease.
- adjuvant therapy in more eduanced stages

② Topical chemotherapy :-

Mechlorethamine
(nitrogen mustard)
- solution, ointment
- S/E : irritation
allergic contact dermatitis
↑ Risk of skin cancer

Carmustine
(BCNU)
- S/E : Telangectasia
myelosuppression
↓
Careful monitoring CBC

③ Radiotherapy :
- Total skin electron beam irradiation (TSEB)
- Local Radiotherapy e X-ray

- preferable → electron beam
  FOR → Single Tumors in ptn e~ plaque stage Disease.

④ **phototherapy** :-

- **UVA** irradiation → following photosenstization with 8-methoxy-psoralen (**PUVA**)
- Broad Band - narrow Band **UVB**
- **UVA1** - Extracorporeal photopheresis (ECP) → in erythrodermic MF
- **PUVA** :-
  - → standard therapy for early stages of MF
  - → maintinance PUVA therapy (every 2-4 weeks) → to prolong remission.
  - → Relapse after Cessation of PUVA OR During maintence ttt → Favors :- CV · Shielded areas as: inner thighs - gluteal cleft

⑧ Systemic therapy ④

[1] Chemotherapy:

+ **Indications** :- unequivocal L.N · Visceral involvemat
- Progressive Skin Tumors → Can't controlled e' Skin targeted Therapy

+ **The Standard ttt** : administration of **6 cycles of CHOP** [Cyclophosphamide Hydroxydaunomycin · Oncovin - Prednisone]

[2] Biological Response modifiers :-

- **Cytokines** : e.g: IFN-α (3-9 million units/3 times/week
  IL-12
- **Retinoids** :- Isotretinoin - etretinate - acitretin
  novel RXR-selective retinoid (Bexarotene)
  - The Drug given orally · Dose 300 mg/m²
  - S/E : Teratogenicity · Hyperlipidemia · Neutropenia Hypothyroidism
- **Immunotoxins** :
  → Denileukin diffitox "ontak" (diphteria toxin linked to IL2)
  Bind to high affenity IL-2 Receptor → expressed By neoplastic-Tcell

- and internalization of the toxin → Result in ↓ inhibition of protien Synthesis and cell Death.

- The Drug given: IV only → to Those whose Malignant Cells express CD25 IL-2 Reptor

- SIE: Toxicity
  - Capillary leak syndrome
  - acute Hypersenstivity - Type Reaction
  - Hypoalbuminemia - Hypotension
- Flu-like Symptoms → for several weeks following infusion

- **Monoclonal antibodies:**
  - Zanolimumab (anti-CD4)
  - alemtuzumab (anti-CD52)

3 Histone deacetylase inhibitor [HDACI]

- new class of Drugs for MF and SS
- Inhibition of enzyme HDAC → affect expression of many gene

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Cutaneous B-cell lymphoma

- ptn with CBCL subdivided into:

1ry
- with only cut. disease
- No evidence of extra-Cutaneous manifistations
- The prognosis → good

2ry
- ↓ 1ry extracut. disease subsequent development of skin lesions
- These Cut. lesions → have the histopathological + immuno-phenotypic feature of original lymphoma
- Poor Prognosis

Classification of primary CBCL (pCBCL)

WHO-EORTC 2005 classification	WHO 2008 classification	Clinical behavior
Primary cutaneous follicle center lymphoma (PCFCL).	Primary cutaneous follicle center lymphoma (PCFCL).	Indolent
Primary cutaneous marginal zone B-cell lymphoma (PCMZL)*.	Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue "MALT lymphoma".	
Primary cutaneous diffuse large B-cell lymphoma, leg type (DLBCLLT).	Primary cutaneous diffuse large B-cell lymphoma, leg type (DLBCLLT).	Intermediate
Primary cutaneous diffuse large B-cell lymphoma, other.	Diffuse large B-cell lymphoma, none otherwise specified.	
Intravascular diffuse large B-cell lymphoma.	Intravascular diffuse large B-cell lymphoma.	

• Common features :-

1 Clinical features :-

- monomorphous - non-Itchy lesions of nodules or tumors (solitary - multiple)
- Deep · Red in color è Smooth surface
- without scaling or ulceration
- lesion arise within short period (1-2 yrs)
- Restricted to Trunk, specially Back
- The extremities or the head and neck.
- peripheral L.N enlargment occur frequently → Early indicating; neoplastic infiltration rather than Dermatopathic lymphadenopathy as in CTCL

2 Non-specific Cut. lesions :

- very uncommon
- varied :- → Herpes Zoster
  - aquired ichthyoses → pruritis
  - → prurigo

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3 Histological features : "B-cell pattern"

- Dense, sharply Demarcated patchy infiltrate "Nodular" in mid or deep dermis, mainly → perivascular → extend to S.C Fat- "Bottom heavy"
- The infiltrate → Spare the epidermis "NO Epidermotropism" and the subepidemal Zone
- The cells tend to → Dissect through Collagen Bundles "Indian file Fashion"

4 phenotyping of the infiltrate : pan-B. cell antigen expression (CD19-20)

Differential diagnosis

	CBCLs	Hodgkin's disease
Early localized nodal disease	Less common "11%"	Common
Specific skin lesions	More common "17%" & they are the initial manifestation in about 5% of cases. They may precede other manifestations by 1-2 years & the prognosis is relatively good.	Very rare, & not in the early disease nor as the only manifestation. Their development worsens the prognosis.
Secondary spread	Occurs to distant sites.	Occurs to contiguous groups of lymph nodes.
Bone marrow involvement	10%	<1%

Main features of primary B-cell lymphomas HL

	Primary cutaneous follicle center lymphoma (Fig. 28)	Primary cutaneous marginal zone B-cell lymphoma (Fig. 29)	Primary cutaneous diffuse large B-cell lymphoma, leg type (Fig. 30)	Intravascular diffuse large B-cell lymphoma
Definition	Neoplastic proliferation of germinal center cells confined to the skin.	This lymphoma is derived from post-germinal center cells.	Characterized by a predominance of large round cells (centroblasts, immunoblasts).	Malignant proliferation of large B-lymphocytes within blood vessels.
Clinical picture	• Asymptomatic solitary or grouped, pink to plum colored papules, plaques or tumors, can be surrounded by patches of erythema. • Ulceration is uncommon. • ***Site:*** Scalp & forehead or the back (lesions located on the back were called Crosti's lymphoma).	• Recurrent asymptomatic pink-violet to red-brown papules, plaques and nodules. • ***Site:*** Extremities (upper more so than lower) or trunk. • Ulceration rarely • Resolution of lesions may be accompanied by secondary anetoderma due to loss of elastic fibers in the area of the tumor infiltrate.	• Almost exclusively in elderly patients, predominantly women. • Solitary or clustered erythematous to red-brown nodules. Small erythematous papules can be seen adjacent to larger nodules. • ***Site:*** Distal aspect of one leg. • Ulceration may occur.	• Indurated, erythematous or violaceous patches & plaques (DD: Panniculitis or vascular tumors). • ***Site:*** Trunk and thighs. The clinical appearance is not typical of cutaneous lymphoma.
Histopathology	• Follicular & diffuse variants. • Neoplastic infiltrate: Centroblasts & centrocytes admixed with immunoblasts, small lymphocytes, histiocytes ± eosinophils & plasma cells. • The infiltrate is mainly in the reticular dermis & subcutis a ***"bottom-heavy"*** lymphocytic infiltrate.	• Nodular or diffuse dermal infiltrates. • Small to medium-sized lymphocytes, lymphoplasmacytoid cells & plasma cells, often with a reactive T-cell infiltrate. • Reactive follicular structures are often present with tumor cells concentrated at their periphery or marginal zone.	• Dense diffuse infiltrate is seen within the dermis and subcutis extending to the dermal epidermal junction. Involvement of the epidermis by clusters of large atypical cells, simulating the Pautrier's microabscesses ***(B-cell epidermotropism).*** • Predominance of large round cells (centroblasts, immunoblasts). • Reactive small lymphocytes are few or absent, & mitoses are frequent.	Proliferation of large atypical lymphocytes that fills dilated blood vessels within the dermis & subcutaneous tissues.

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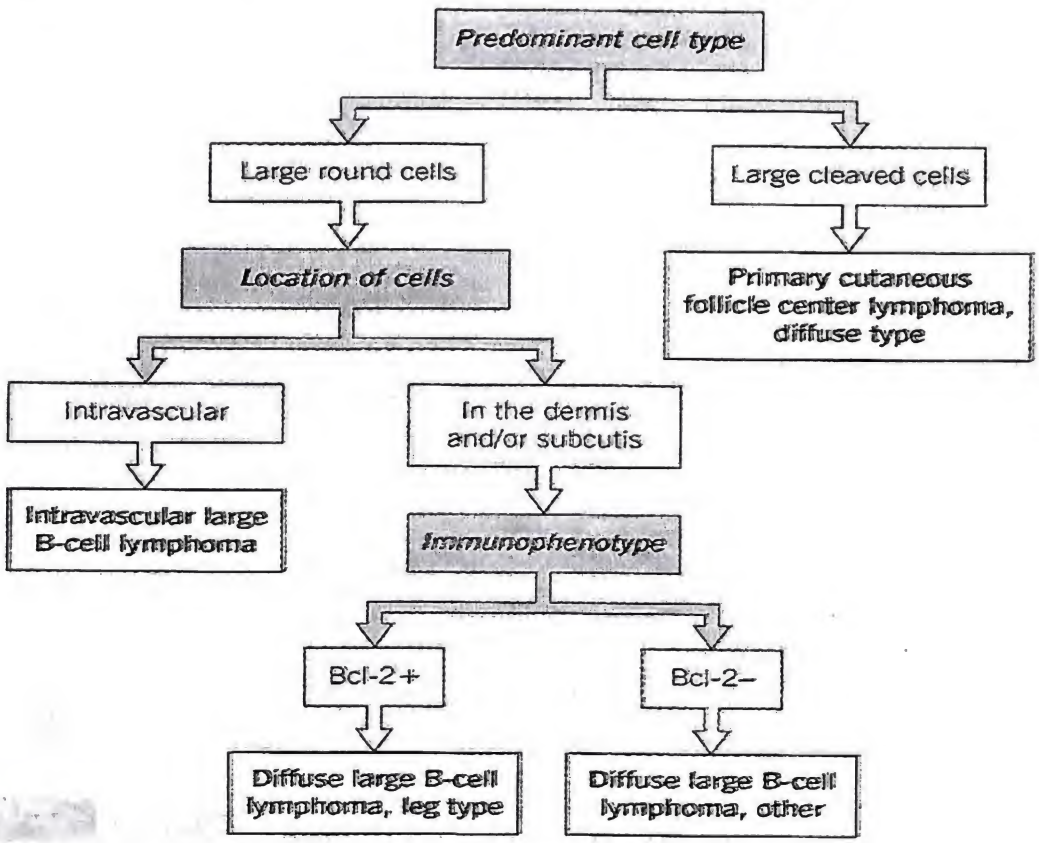
Main features of primary B-cell lymphomas *(Cont'd)*

	Primary cutaneous follicle center lymphoma	Primary cutaneous marginal zone B-cell lymphoma	Primary cutaneous diffuse large B-cell lymphoma, leg type	Intravascular diffuse large B-cell lymphoma
Markers	• ***+ve:*** Monotypic surface immunoglobulins (either κ or λ light chains) – B-cell-associated antigens (CD20, CD79a) – Bcl-6 (a marker of germinal center cells & other blastic cells) & – CD 10. • ***-ve:*** bcl-2.	• ***+ve for:*** Monotypic surface immunoglobulins (either κ or λ light chains) – B-cell-associated antigens (CD20, CD79a) – Bcl-2. • ***-ve for:*** CD5, CD10 and Bcl-6.	• Monoclonal surface or cytoplasmic immunoglobulins. • ***+ve for:*** B-cell markers (CD20, CD79a), Bcl-2, MUM1 (multiple myeloma oncogene 1) & FOX-P1.	• ***+ve for:*** B-cell-associated markers – Bcl-2, MUM1 & FOX-P1. • Staining with endothelial cell-related antibodies (e.g. CD31, CD34) highlights the characteristic intravascular location of the cells.
Treatment	• Superficial radiotherapy is the treatment of choice. • Extensive cutaneous involvement: Chlorambucil or combination chemotherapy.	• Radiotherapy. • If associated with Borrelia burgdorferi: Antibiotic therapy. • Multifocal disease: Chlorambucil.	• Solitary lesions: Radiotherapy. Intralesional rituximab may be effective. • Multifocal lesions: Antimalignant chemotherapy.	Systemic chemotherapy plus rituximab is the treatment of choice.
Prognosis	Favorable.	Excellent.	Less favorable.	The prognosis of cases limited to the skin is better than that of the systemic (disseminated) form.

ıch to the diagnosis of cutaneous large B-cell lymphomas* HL



• Pathogenesis: factor play Role etiology → Local ttt combined Systemic Chemotherapy

1- Longstanding antigenic Stimulation :-

D.t chronic infection è specific microorganism

↔ B-Cell lymphoma → arising in Gastric mucosa

↓

[Mucosal Association Lymphoid Tissue or MALT Lymphoma]

: Helicobacter pylori

↔ Borrelia burgdoferi

↔ AIDS

↔ EBV in Burkitt's lymphoma

2- Reversible Iry CBCL → observed in pts undergoing Therapy e- MTX → Suggesting → immune Dysregulation play a role in develop Disease

• Treatment

① Radiotherapy ② excision of skin lesion → when there is No extra Cutan. affection

③ if extra Cut involvment occur →

Differential diagnosis between CBCL & CTCL

	CBCL	CTCL
Clinical		
History	Short (1-2 years)	Long (5-20 years)
Skin lesions	• Often solitary or multiple monomorphous lesions: Nodules or tumors without scaling or ulceration, rapidly growing. • Deep red in color. • Usually localized in the head, trunk or extremities.	• Multiple & polymorphous lesions: Patches, plaques & tumors with scaling & ulceration, slowly growing. • Yellow-brown or pinkish. • Widespread.
Lymph nodes • Neoplastic • Dermatopathic	 • Frequent & early. • Rare & late.	 • Rare & late. • Frequent & early.
Bone marrow involvement	• Not rare.	• Rare.
Extracutaneous affection	• Early → bad prognosis.	• Late.
Histopathology	***B-cell pattern "nonepidermotropic"***	***T-cell pattern "epidermotropic"***
Epidermis	Normal or atrophic	Often acanthotic
The infiltrate	• Middle & deep dermis. • Sharp nodular. • Perivascular. • Monomorphous infiltrate of lymphocytes, lymphoplasmacytoid cells or small & large follicle center cells.	• Upper & middle dermis. • Diffuse band-like. • Periappendageal. • Polymorphous infiltrate of Sézary cells, mycosis cells and macrophages, eosinophils & plasma cells.
Subepidermal zone	Free.	Involved with pronounced edema.
Post-capillary venules	No proliferation.	Proliferation.
Functional		
Patchy acid phosphatase & acid esterase	No	Present.
Cell surface markers	B-cells.	T-cells.
Monoclonal intracytoplasmic Ig production	Present.	Absent.

Other Lymphoproliferative & Myeloproliferative s

1 Hodgkin's Disease :

- Disease of lymphatic System
- initially limited → to single group of L.N
- Spreading → through lymphatic vessels to contagious groups of L.N.

A Staging Classifications

- Vascular invasion within L.N → Hematogenous spread to Distant L.N, or extranodal sites → widespread Disease (Rarely involve Skin)
- Retrograde lymphatic spread → involvment of Liver Lung - Skin

- Stage I :- involvement of single L.N Region
- Stage II :- involvment of 2 or more L.N Regions on the Same side of Diaphragm
- Stage III :- Involvment of L.N Region. on Both Sides of Diaphragm
  - accompanied By: involve Spleen
- Stage IV : Disseminated involvment of extra-Lut organs :- Bone marrow, Lung - Liver, Bone, Skin

★ All stages subDivided into :- A - B
(Absconce or Presence of systemic symptoms)

B Histopathology :-

- Presence of Reed-Sternberg cells essential for histologic Diagnosis
- Large 15 to 60 µm in Diameter
  Contain several nuclei
  - one multilobular nucleus
  OR
  - bilobed mirror-image nucleus
- The nucleoli : Large eosinophilic
  Surrounded By: Clear halo
- Polymorphous infiltrate of :
  - lymphocytes
  - polymorph nuclear leukocytes
  - eosinophils
  - plasma cells
  - Histiocytes
  - fibroblasts

C Cutaneous manifestations :-

① Non-specific lesion: v. common

↳ **Pruritus**: ± pigmentation, prurigo that start on the **Legs**.
pruritus → precede the Diagnosis may be the only symptom

↳ **Aquired Ichthyosis**: starting on Legs

↳ **Herpes Zoster**: generalized

↳ Alopecia, exfoliative Dermatitis
Erythema nodosum

② Specific Lesions: V. Rare

- Consist of: nodules, plaques → undergo → Ulceration
- most pts → Die within few months → following the development of specific skin Lesion

3- Specific skin lesion:
Radiotherapy - chemotherapy

D Rye classification : Depending on cell type

1- lymphocyte predominance] → good prognosis
2- Nodular sclerosing]
3- Mixed Cellularity] → poor prognosis
4- lymphocyte depleted]

E pathogenesis

- Reed-Sternberg cells → derived from transformed T-helper lymphocytes.
They are Regularly Reacted with monoclonal antigen
Ki-1 → which React ± Transformed T-helper cells
- Ki-1 antigen → Not specific for Hodgkin's disease.
  - Found also in: Large cell anaplastic lymphomas Consisting about 8% of non-Hodgkin's lymphoma.
    - lymphomatoid papulosis
    - Immunoblastic Lymphadenopathy.
- in Contrast to the T-lymphocytes → The B-lymphocytes Not affected in Hodgkin's disease

F Treatment :-

1- non-specific skin lesion → Symptomatically
2- pruritus → Antihistamines - UVB - PUVA

2 Multiple Myeloma: [plasmacytoma / Monoclonal Gammopathy] سؤال 2-1

- **D.f:** Disease of Bone marrow Resulting from: clonal expansion of neoplastic plasma cells. with monoclonal production of paraproteins (IgG 50% - IgA 25%)
- **Cutaneous manifestations:-**

1 Non-Specific Lesions:

1- Diffuse normolipemic plane xanthoma
2- Primarly systemic amyloidosis
3- Cryoglobulinemia
4- Pyoderma gangrenosum
5- Disseminated Filiform Hyperkeratosis Commonly on Face "Nazzaro sign"
6- Scleromyxedema
7- Acquired Ichthyosis, Pruritas, opportunistic infections

2 Specific Lesions:

1- Primary Cutaneous plasmacytoma:-
V. rare, Solitary, multiple papules nodules

2- 2ry Skin involument :-
- occur in 10% of Cases
- violaceous nodules or firm-dome shape Tumors → Develop late in the Course of the Disease.
  ↳ Should Regarded as: Bad prognostic Sign
- Histopathology :- (Low grade CBCL)
Beneath Flattened epidermis → There is Nodular perivascular dense infiltrate, mostly → ATypical plasma cells without Epidermotropism

- **Diagnosis:-**

1- monoclonal gammopathy in serum (M protien) paraprotinuria (Bence-Jones Test)
2- Biobsy of Bone marrow → ATypical plasma Cells
3- Osteolytic Bone lesions + 2ry changes
Caused By :- monoclonal gammopathy

- **Treatment:-**

1- Chemotherapeutic agents < mono / poly chemotherapy
2- Bone marrow Transplant

3 Cutaneous leukemias :- [leukemia Cutis] → Malignant Neoplasm of WBCs

- **3 major groups:**

1- lymphocytic → Acute (ALL) / Chronic (CLL)
2- Granulocytic → Acute · chronic
3- Monocytic - myelomonocytic

non-specific Skin lesion (Leukemids)	Specific skin lesion
e.g:- generalized Pruritus - prurigo-like papules - Erythroderma - Disseminated HZ - petiche - ecchymosis	- more in Chronic lymphocytic leukemia - Nodular - Diffuse - plaque-like infiltration - macules - ecchymoses - palpable purpura. - Erythroderma "specific" - ulcerative lesions

- **Monocytic - Myelomonocytic leukemia**
  - ch.ch feature → Gingival Hypertrophy
  - ttt → Ionizing Radiation - Chemo

- **Lymphocytic Leukemia :-**
  - Specific Skin lesion - more in Chronic Type
  - occur more in :- Face "Leonine Face"
  - Erythroderma ; Bullous lesions → only è CLL
  - Histopathology :-
    - the infiltrate composed of small-mature lymphocytes with only occasional Mitosis
    - Rarely: T and B lymphocytes → è Corebriform nuclei and Epidermotropism

- **Granulocytic Leukemia :**
  - One or more specific Tumors "granulocytic Sarcomas" Chloroma"
  - enzyme "Myeloperoxidase" → Cause green pigment which is visible on Cut surface of tumors
  - 2 dermatosis precede acute granulocytic or myelomonocytic leukemia :-
    - pyodema gangrenosum
    - Sweet's syndrome.

4 Pseudolymphomas :-

- D.f : Benign - persistent Lymphoid Proliferation in the Dermis.
  - Difficult to distinguish from : Low grade malignant lymphoma
  - rarely : Transform to Lymphoma

- HistoPathology :
  1 - presence of T - OR B Lymphoid proliferation
  2 - few mitotic figures
  3 - may be subtle nuclear atypia
  4 - T-Cell pseudolymphoma : Band like OR nodular , B-Cell pseudolymphoma : Nodular
  5 - Germinal Center formation → Absent in B-Cell pseudo , T Cell pseudo → No epidemotropism

T-Cell pseudolymphomas

1 - Actinic Reticuloid
2 - Parapsoriasis
3 - Jessner's Lymphocytic infiltrate
4 - Persistant Contact Dermatitis
5 - Persistant nodular Scabies and Insect Bite
6 - Silicone Breast implant
7 - Drug Reactions :-
  - anticonvulsants
  - ACE inhibitors
  - B-Blockers
  - Cytotoxics
  - antibiotics

B-Cell pseudolymphoma

1 - lymphocytoma Cutis
2 - Lyme Disease
3 - Tattoos
4 - After vaccination OR Trauma
5 - Accupuncture
6 - Scars of Herpes Zoster

- Clinical picture :-
  - Both present as multiple Skin nodules as in :-
    - persistant nodular Scabies
    - lymphocytoma Cutis
  - T-Cell pseud → Erythroderma as in :
    - Drug Reaction
    - Contact Dermatitis
  - B-Cell pseud → associated w/ palpable lymphadenopathy

- Managment :-
  - The Cause → should Removed if possible
  - symptomatic ttt for Itching :
    - Topical steroid → will accelerate clearance.

[5] Benign Lymphocytic infiltrate of Jessner:

- **Ch.ch By:**
  - asymptomatic, well-demarcated - slight infiltrated, smooth Erythematous Nodules and plaques, Central clearing
  - Located: on Face
  - it heals: after several months or years
  - without Scarring
  - Recurrences → may occur
  - lesion aggrevated By → Sun
- **Histopathology:-**
  - Beneath Anormal or slightly flattened epidermis → There is perivascular periappendegeal patchy lymphocytic infilhat in the Dermis
  - lymphoid follicles → Not present
  - the infiltrate → T-cell process
- **Treatment:** 1-Topical, intralesional Steroid
  2- Anti-malarials

[6] Lymphocytoma Cutis:-

[pseudolymphoma of spiegler-Fendt]
[lymphadenosis benigna Cutis] بنزيون

- → affect more: women → Site:- Face (ear)
- → lesion: Solitary papule - Nodule, plaque as grouped lesion
  OR as numerous Disseminated lesion
- Asymptomatic - firm - Skin colored Red or Violaceous
- → Heal → Spontenously
  - → may persist for months or yrs.
  - → may be recurrence.
- → some Cases associated e` Lyme disease
- → Histopathology:
  1- heavy Dermal infiltrate → separated from epidermis By: narrow Grenz Zone of normal Collagen
  2- The infiltrate consist of: 2 Types of Cells Small and Large lymphocytes

- which lie :- intermingled with one another
OR in Follicular arrangment , as in: malignant lymphoma → at periphery of the infiltrate :- single rows of lymphocytes extending B.tween collagen Bundles " Indian's in a file"

- treatment

1- Topical
OR Intralesional
Steroid
2- Radiotherapy
3- Penicillin

DD between idiopathic pseudo-T-cell lymphomas with a band-like pattern & MF

	MF-like pseudo-TCL	MF
Presentation	Solitary/several lesions.	Generalized.
Epidermotropism	Absent/moderate.	Prominent.
Pautrier's microabscesses	Generally absent.	Often present.
Cerebriform mononuclear cells	Mainly medium-sized.	Medium-sized/large.
Loss CD2, CD3 or CD5	Not reported.	Variable.
Clinical course	Spontaneous remissions or complete cure after local therapy.	Progressive.

DD between cutaneous B-cell lymphoma (CBCL) & pseudolymphomas (PL)

	CBCL (%)	PSL (%)
Clinical		
Number, distribution & localization of skin lesions	Solitary or multiple & generalized monomorphous (100%).	Solitary, head (80%).
Extracutaneous involvement	Present (100%)	Absent (100%).
Type & response to therapy	Aggressive, TR.	Nonaggressive, CR.
Fatal outcome	Likely.	No.
Recurrences	Always.	Rare (<10%).
Cure	Not possible.	Possible.
Survival time	Affected.	Normal.
Histologic		
Infiltrate covering all levels of the dermis	Mostly (>70%).	Rarely (<5%).
Pattern of infiltrate	Diffuse or nodular, bottom>top, heavy.	Nodular (>90%), top>bottom, heavy.
Follicular center formation (Hx & E)	Usually absent.	Usually present.
Transformation into blast form (centroblastic, immunoblastic)	May occur.	Never occurs.
Eosinophilic granulocytes	Usually absent.	Always present.
Phenotypical		
Monotypic kappa or lambda light chain reaction of surface immunoglobulin	Present (100%).	Absent (100%).
% of cells expressing B-cell markers (CD20, MB2, CD45R)	High (>50%).	Medium (50% or less).
T-cell markers (CD43, CD45RA, CD45RO)	Low (<50%).	Medium (50% or more).
Network of CD21 +ve dendritic reticulum cells	Mostly absent.	Mostly present, regular.

- Plague stage MF (diagnosis, ttt). (2012).
- Mycosis fungides (enumerate different clinical presentations, enumerate lines of skin targeted ttt). (2011).
- Different clinical presentations of mycosis fungoides. (2010).
- Clinical types of mycosis fungoides – management (2007 - 1983).
- Investigations and ttt of patch stage mycosis
- Investigations and ttt of patch stage mycosis fungoides involving less than 10% body surface area. (2009).
- Diagnosis of mycosis fungoides – the 6 histopathological criteria for the diagnosis of MF (2003 - 1984)
- Mycosis fungoides; Histopathological features (2001).
- CP and histopathology of different types of cutaneous T-cell lymph. (2010).
- Cutaneous T- cell lymphoma (1995).

Lymphoma:

1. Clinical picture of MF
2. Stages & ttt of MF
3. Lymphomatosus papulosis
4. SC panniculitis T-cell lymphoma
5. Role of dermatologist in diagnosis of Hodgkin's
6. Malignant lymphoma vs pseudolymphoma
7. Lymphocytic infiltrate of Jessenervs lymphocytoma cutis

8. Histopathology of MF

-Dusky Red papulo nodular lesion:

1. MF
2. EN
3. LE
4. Rosacea
5. Kapssi Sarcoma
6. Granuloma facial
7. Sarcoidosis
8. Lupus vulgaris

-Band-like infiltrate:

1. MF
2. 2ry syphilis
3. Fungus
4. LP
5. lichenoid eruption

-Hypopigmented MF:

1. Child
2. Back - Buttocks

-Cigarrate paper Scar:

1. MF
2. 3ry syphillis
3. Ehler-Danlos
4. LS
5. Stia Distensae
6. Poikilodema atrophicans Vasculare

-Red Face:

1. Flushing
2. Rosacea
3. Dematitis CAD-CD. SD. actinic
4. Erysipeles
5. CTD:- LE, DM
6. Metabolic: prophyria
7. Genet- XP. Bloom's
8. Lymphoma

-Indians in a file:

pseudolymphoma

-Leonine facies:

1. lymphoma Cutis
2. Nodular Masticytosis
3. Histiocytosis
4. Actinic Dematitis
5. Sarcoidosis
6. leismaniasis
7. Leukemia Cutis
8. Scleromyxedema

-Grenz Zone:

1. Setary Syndrom
2. LL
3. Granuloma facial
4. lymphocytoma Cutis

-Skin Disease of Breast + Nipple:

1. MF
2. Candidiasis
3. leiomyomas
4. Lupus panniculitis
5. BCC - Breast cancer
6. Bacterial mastitis
7. Acanthosis Nigica
8. Morphea
9. Darier Disease
10. Neurofibroma

-Skin Disease of groin:

1. MF
2. Candidiasis
- lang cell Histiocytosis
- psoriasis

Inverse pityriasis Rosea
penphigous follicularis
Seb. Dematitis
Contact Dematitis